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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	4	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	5	MAR 02	GBFULL: New full-text patent database on STN
NEWS	6	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 22	KOREAPAT now updated monthly; patent information enhanced
NEWS	9	MAR 22	Original IDE display format returns to REGISTRY/ZREGISTRY
NEWS	10	MAR 22	PATDPASPC - New patent database available
NEWS	11	MAR 22	REGISTRY/ZREGISTRY enhanced with experimental property tags
NEWS	12	APR 04	EPFULL enhanced with additional patent information and new fields
NEWS	13	APR 04	EMBASE - Database reloaded and enhanced
NEWS	14	APR 18	New CAS Information Use Policies available online
NEWS	15	APR 25	Patent searching, including current-awareness alerts (SDIs), based on application date in CA/CAplus and USPATFULL/USPAT2 may be affected by a change in filing date for U.S. applications.
NEWS	16	APR 28	Improved searching of U.S. Patent Classifications for U.S. patent records in CA/CAplus
NEWS	17	MAY 23	GBFULL enhanced with patent drawing images
NEWS	18	MAY 23	REGISTRY has been enhanced with source information from CHEMCATS
NEWS	19	JUN 06	The Analysis Edition of STN Express with Discover! (Version 8.0 for Windows) now available
NEWS	20	JUN 13	RUSSIAPAT: New full-text patent database on STN
NEWS	21	JUN 13	FRFULL enhanced with patent drawing images
NEWS	22	JUN 27	MARPAT displays enhanced with expanded G-group definitions and text labels
NEWS	23	JUL 01	MEDICONF removed from STN
NEWS	24	JUL 07	STN Patent Forums to be held in July 2005
NEWS	25	JUL 13	SCISEARCH reloaded
NEWS	26	JUL 20	Powerful new interactive analysis and visualization software, STN AnaVist, now available

NEWS EXPRESS JUNE 13 CURRENT WINDOWS VERSION IS V8.0, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005

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NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items

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FILE 'HOME' ENTERED AT 19:27:35 ON 02 AUG 2005

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

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DICTIONARY FILE UPDATES:    1 AUG 2005  HIGHEST RN 857935-17-2

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**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
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Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
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http://www.cas.org/ONLINE/DBSS/registryss.html

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Uploading C:\Program Files\Stnexp\Queries\10759345.str
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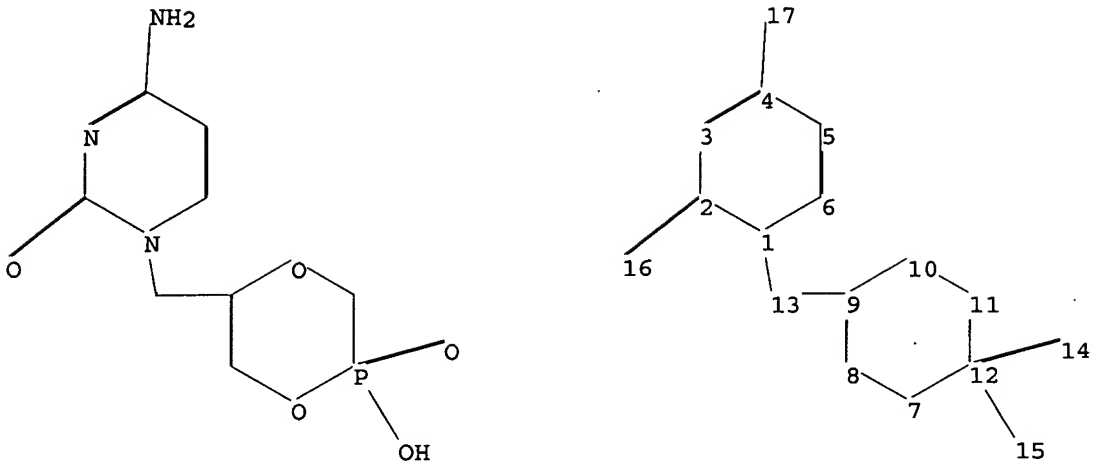

chain nodes :
13 14 15 16 17
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
1-13 2-16 4-17 9-13 12-14 12-15
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-6 1-13 2-3 2-16 3-4 4-5 4-17 5-6
exact bonds :
7-8 7-12 8-9 9-10 9-13 10-11 11-12
normalized bonds :
12-14 12-15
isolated ring systems :
containing 1 : 7 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS

L1 STRUCTURE UPLOADED

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SAMPLE SEARCH INITIATED 19:28:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 8 TO ITERATE

100.0% PROCESSED 8 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 8 TO 329
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED -     121 TO ITERATE

100.0% PROCESSED      121 ITERATIONS                                 4 ANSWERS
SEARCH TIME: 00.00.01

L3             4 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   161.33     161.54

FILE 'CAPLUS' ENTERED AT 19:28:29 ON 02 AUG 2005
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FILE COVERS 1907 - 2 Aug 2005  VOL 143 ISS 6
FILE LAST UPDATED: 1 Aug 2005  (20050801/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s l3
L4           46 L3

=> s l4 and (alkylglycerol or alkylpropanediol or alkylthioglycerol or
alkoxyalkanol or alkylethanediol)
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            160 ALKYLGLYCEROLS
            290 ALKYLGLYCEROL
                  (ALKYLGLYCEROL OR ALKYLGLYCEROLS)
             21 ALKYLPROPANEDIOL
             12 ALKYLPROPANEDIOLS
             31 ALKYLPROPANEDIOL
                  (ALKYLPROPANEDIOL OR ALKYLPROPANEDIOLS)
              2 ALKYLTHIOGLYCEROL
             93 ALKOXYALKANOL
             77 ALKOXYALKANOLS
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                  (ALKOXYALKANOL OR ALKOXYALKANOLS)
              3 ALKYLETHANEDIOL
              3 ALKYLETHANEDIOLS
              5 ALKYLETHANEDIOL
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L5 3 L4 AND (ALKYLGLYCEROL OR ALKYLPROPANEDIOL OR ALKYLTHIOGLYCEROL OR ALKOXYALKANOL OR ALKYLETHANEDIOL)

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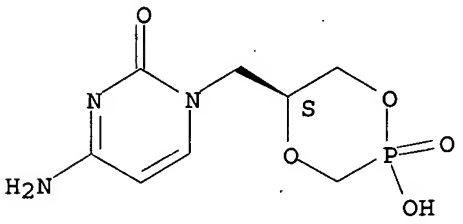
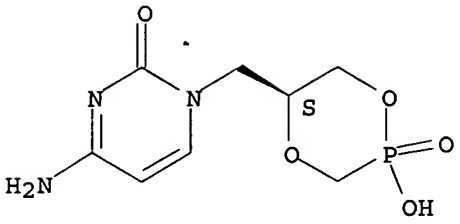
L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:129464 CAPLUS
DOCUMENT NUMBER: 142:366750
TITLE: Comparison of the antiviral activities of alkoxyalkyl and alkyl esters of cidofovir against human and murine cytomegalovirus replication in vitro
AUTHOR(S): Wan, William B.; Beadle, James R.; Hartline, Caroll; Kern, Earl R.; Ciesla, Stephanie L.; Valiaeva, Nadejda; Hostetler, Karl Y.
CORPORATE SOURCE: Veterans Administration San Diego Healthcare System and the Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0676, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2005), 49(2), 656-662
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **127757-45-3 849177-08-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(comparison of antiviral activities of alkoxyalkyl and alkyl esters of cidofovir against human and murine cytomegalovirus replication in vitro)
RN 127757-45-3 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 849177-08-8 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]-, dihydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 H_2O

AB Alkoxyalkyl esters of cidofovir (CDV) have substantially greater antiviral activity and selectivity than unmodified CDV against herpesviruses and orthopoxviruses in vitro. Enhancement of antiviral activity was also noted when cyclic CDV was esterified with **alkoxyalkanols.** In vitro antiviral activity of the most active analogs against human cytomegalovirus (HCMV) and orthopoxviruses was increased relative to CDV up to 1000- or 200-fold, resp. Alkyl chain length and linker structure are important potential modifiers of antiviral activity and selectivity. In this study, the authors synthesized a series of alkoxyalkyl esters of CDV or cyclic CDV with alkyl chains from 8 to 24 atoms and having linker moieties of glycerol, propanediol, and ethanediol. The authors also synthesized alkyl esters of CDV which lack the linker to determine if the alkoxyalkyl linker moiety is required for activity. The new compds. were evaluated in vitro against HCMV and murine CMV (MCMV). CDV or cyclic CDV analogs both with and without linker moieties were highly active against HCMV and MCMV, and their activities were strongly dependent on chain length. The most active compds. had 20 atoms esterified to the phosphonate of CDV. Both alkoxypropyl and alkyl esters of CDV provided enhanced antiviral activities against CMV in vitro. Thus, the oxypropyl linker moiety is not required for enhanced activity. CDV analogs having alkyl ethers linked to glycerol or ethanediol linker groups also demonstrated increased activity against CMV.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:218837 CAPLUS

DOCUMENT NUMBER: 139:239732

TITLE: Increased antiviral activity of 1-O-hexadecyloxypropyl-[2-14C]cidofovir in MRC-5 human lung fibroblasts is explained by unique cellular uptake and metabolism

AUTHOR(S): Aldern, Kathy A.; Ciesla, Stephanie L.; Winegarden, Kristine L.; Hostetler, Karl Y.

CORPORATE SOURCE: Department of Medicine, San Diego VA Healthcare System and the University of California, La Jolla, CA, USA

SOURCE: Molecular Pharmacology (2003), 63(3), 678-681
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

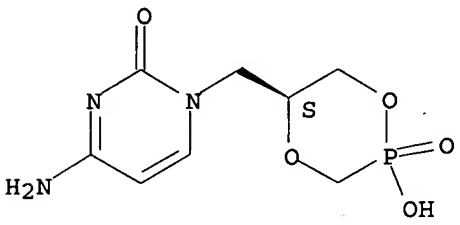
IT **127757-45-3**
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(notincreased antiviral activity of 1-O-hexadecyloxypropyl-[2-

14C]cidofovir in MRC-5 human lung fibroblasts is explained by unique cellular uptake and metabolism)

RN 127757-45-3 CAPLUS

CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Recently, there has been renewed interest in finding orally active drugs against smallpox. Cidofovir (CDV) given by parenteral injection has been shown to protect against lethal poxvirus infection. We have been interested in the synthesis and evaluation of orally active derivs. of CDV. Previous studies showed that the CDV and cyclic cidofovir (cCDV) analogs 1-O-hexa-decyloxypropyl-CDV (HDP-CDV) and 1-O-hexadecyloxypropyl-cCDV (HDP-cCDV), show >100-fold increases in antiviral activity vs. the unmodified nucleosides against cells infected with orthopoxviruses, cowpox, and vaccinia virus. In contrast to CDV, HDP-CDV is orally bioavailable and has been reported to be orally active in lethal cowpox virus infection in mice. To assess the metabolic basis for the increased antiviral activity of HDP-CDV in vitro, we studied the cellular uptake and anabolic metabolism of 14C-labeled CDV, cCDV, and their **alkoxyalkanol** esters HDP-CDV and HDP-cCDV. HDP-CDV and HDP-cCDV were taken up rapidly by MRC-5 human lung fibroblasts in vitro, but uptake of CDV and cCDV was much slower. Anal. of cellular metabolites showed that levels of cidofovir diphosphate (CDV-DP), the active antiviral compound, were >100 times greater with HDP-CDV than levels observed with CDV. When cells were exposed to HDP-CDV, the intracellular half-life of CDV-DP was 10 days vs. 2.7 days reported when cells are exposed to CDV. HDP-CDV seems to circumvent poor cellular uptake by rapid association with cellular membrane phospholipids, whereas CDV uptake proceeds via the slow process of fluid endocytosis.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:240052 CAPLUS

DOCUMENT NUMBER: 137:134473

TITLE: Enhanced inhibition of orthopoxvirus replication in vitro by alkoxyalkyl esters of cidofovir and cyclic cidofovir

AUTHOR(S): Kern, Earl R.; Hartline, Caroll; Harden, Emma; Keith, Kathy; Rodriguez, Natalie; Beadle, James R.; Hostetler, Karl Y.

CORPORATE SOURCE: University of Alabama School of Medicine, Birmingham, AL, USA

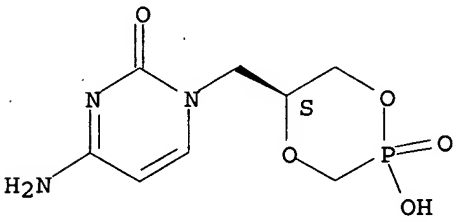
SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(4), 991-995
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:134473
IT **127757-45-3P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(enhanced inhibition of orthopoxvirus replication in vitro by alkoxyalkyl esters of cidofovir and cyclic cidofovir)
RN 127757-45-3 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The nucleotide phosphonates cidofovir (CDV) and cyclic cidofovir (cCDV) are potent antiviral compds. when administered parenterally but are not well absorbed orally. These compds. have been reported to have activity against orthopoxvirus replication in vitro and in animal models when administered parenterally or by aerosol. To obtain better oral activity, we synthesized a novel series of analogs of CDV and cCDV by esterification with two long-chain **alkoxyalkanols**, 3-hexadecyloxy-1-propanol (HDP-CDV; HDP-cCDV) or 3-octadecyloxy-1-ethanol (ODE-CDV; ODE-cCDV). Their activities were evaluated and compared with those of CDV and cCDV in human foreskin fibroblast (HFF) cells infected with vaccinia virus (VV) or cowpox virus (CV) using a plaque reduction assay. The 50% effective concns. (EC50s) against VV in HFF cells for CDV and cCDV were 46.2 and 50.6 μM compared with 0.84 and 3.8 μM for HDP-CDV and HDP-cCDV, resp. The EC50s for ODE-CDV and ODE-cCDV were 0.20 and 1.1 μM, resp. The HDP analogs were 57- and 13-fold more active than the parent nucleotides, whereas the ODE analogs were 231- and 46-fold more active than the unmodified CDV and cCDV. Similar results were obtained using CV. Cytotoxicity studies indicated that although the analogs were more toxic than the parent nucleotides, the selective index was increased by 4- to 13-fold. These results indicate that the alkoxyalkyl esters of CDV and cCDV have enhanced activity in vitro and need to be evaluated for their oral absorption and efficacy in animal models.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s l3 or cyclic cidovoir
          46 L3
      291904 CYCLIC
         332 CYCLICS
      292034 CYCLIC
                (CYCLIC OR CYCLICS)
           0 CIDOVOIR
           0 CYCLIC CIDOVOIR
                (CYCLIC(W)CIDOVOIR)
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```
L6          46 L3 OR CYCLIC CIDOVOIR

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alkoxyalkanol or alkylethanediol)
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           160 ALKYLGLYCEROLS
           290 ALKYLGLYCEROL
                 (ALKYLGLYCEROL OR ALKYLGLYCEROLS)
            21 ALKYLPROPANEDIOL
            12 ALKYLPROPANEDIOLS
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                 (ALKYLPROPANEDIOL OR ALKYLPROPANEDIOLS)
             2 ALKYLTHIOGLYCEROL
            93 ALKOXYALKANOL
            77 ALKOXYALKANOLS
           139 ALKOXYALKANOL
                 (ALKOXYALKANOL OR ALKOXYALKANOLS)
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             5 ALKYLETHANEDIOL
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L7           3 L6 AND (ALKYLGLYCEROL OR ALKYLPROPANEDIOL OR ALKYLTHIOGLYCEROL
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L8          46 L4 OR CYCLIC CIDOVOIR

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             2 ALKYLTHIOGLYCEROL
            93 ALKOXYALKANOL
            77 ALKOXYALKANOLS
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L9           3 L8 AND (ALKYLGLYCEROL OR ALKYLPROPANEDIOL OR ALKYLTHIOGLYCEROL
               OR ALKOXYALKANOL OR ALKYLETHANEDIOL)

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L9   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:129464  CAPLUS
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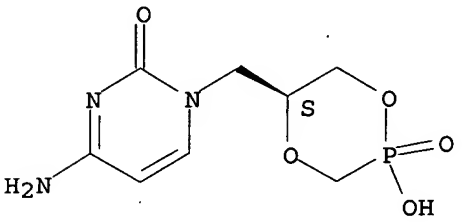
DOCUMENT NUMBER: 142:366750
TITLE: Comparison of the antiviral activities of alkoxyalkyl and alkyl esters of cidofovir against human and murine cytomegalovirus replication in vitro
AUTHOR(S): Wan, William B.; Beadle, James R.; Hartline, Caroll; Kern, Earl R.; Ciesla, Stephanie L.; Valiaeva, Nadejda; Hostetler, Karl Y.
CORPORATE SOURCE: Veterans Administration San Diego Healthcare System and the Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0676, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2005), 49(2), 656-662
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **127757-45-3 849177-08-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(comparison of antiviral activities of alkoxyalkyl and alkyl esters of cidofovir against human and murine cytomegalovirus replication in vitro)

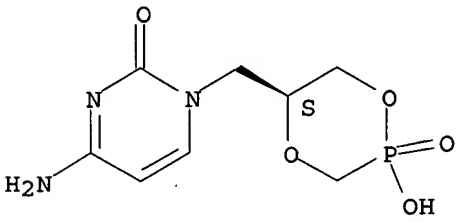
RN 127757-45-3 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 849177-08-8 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]-, dihydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 H_2O

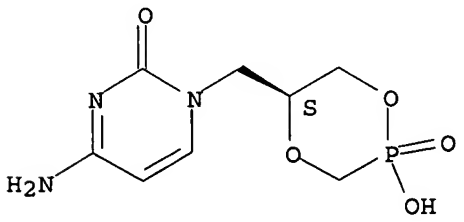
AB Alkoxyalkyl esters of cidofovir (CDV) have substantially greater antiviral activity and selectivity than unmodified CDV against herpesviruses and orthopoxviruses in vitro. Enhancement of antiviral activity was also

noted when cyclic CDV was esterified with **alkoxyalkanols**. In vitro antiviral activity of the most active analogs against human cytomegalovirus (HCMV) and orthopoxviruses was increased relative to CDV up to 1000- or 200-fold, resp. Alkyl chain length and linker structure are important potential modifiers of antiviral activity and selectivity. In this study, the authors synthesized a series of alkoxyalkyl esters of CDV or cyclic CDV with alkyl chains from 8 to 24 atoms and having linker moieties of glycerol, propanediol, and ethanediol. The authors also synthesized alkyl esters of CDV which lack the linker to determine if the alkoxyalkyl linker moiety is required for activity. The new compds. were evaluated in vitro against HCMV and murine CMV (MCMV). CDV or cyclic CDV analogs both with and without linker moieties were highly active against HCMV and MCMV, and their activities were strongly dependent on chain length. The most active compds. had 20 atoms esterified to the phosphonate of CDV. Both alkoxypropyl and alkyl esters of CDV provided enhanced antiviral activities against CMV in vitro. Thus, the oxypropyl linker moiety is not required for enhanced activity. CDV analogs having alkyl ethers linked to glycerol or ethanediol linker groups also demonstrated increased activity against CMV.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:218837 CAPLUS
DOCUMENT NUMBER: 139:239732
TITLE: Increased antiviral activity of 1-O-hexadecyloxypropyl-[2-14C]cidofovir in MRC-5 human lung fibroblasts is explained by unique cellular uptake and metabolism
AUTHOR(S): Aldern, Kathy A.; Ciesla, Stephanie L.; Winegarden, Kristine L.; Hostetler, Karl Y.
CORPORATE SOURCE: Department of Medicine, San Diego VA Healthcare System and the University of California, La Jolla, CA, USA
SOURCE: Molecular Pharmacology (2003), 63(3), 678-681
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **127757-45-3**
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(notincreased antiviral activity of 1-O-hexadecyloxypropyl-[2-14C]cidofovir in MRC-5 human lung fibroblasts is explained by unique cellular uptake and metabolism)
RN 127757-45-3 CAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Recently, there has been renewed interest in finding orally active drugs against smallpox. Cidofovir (CDV) given by parenteral injection has been shown to protect against lethal poxvirus infection. We have been interested in the synthesis and evaluation of orally active derivs. of CDV. Previous studies showed that the CDV and cyclic cidofovir (cCDV) analogs 1-O-hexa-decyloxypropyl-CDV (HDP-CDV) and 1-O-hexadecyloxypropyl-cCDV (HDP-cCDV), show >100-fold increases in antiviral activity vs. the unmodified nucleosides against cells infected with orthopoxviruses, cowpox, and vaccinia virus. In contrast to CDV, HDP-CDV is orally bioavailable and has been reported to be orally active in lethal cowpox virus infection in mice. To assess the metabolic basis for the increased antiviral activity of HDP-CDV in vitro, we studied the cellular uptake and anabolic metabolism of 14C-labeled CDV, cCDV, and their **alkoxyalkanol** esters HDP-CDV and HDP-cCDV. HDP-CDV and HDP-cCDV were taken up rapidly by MRC-5 human lung fibroblasts in vitro, but uptake of CDV and cCDV was much slower. Anal. of cellular metabolites showed that levels of cidofovir diphosphate (CDV-DP), the active antiviral compound, were >100 times greater with HDP-CDV than levels observed with CDV. When cells were exposed to HDP-CDV, the intracellular half-life of CDV-DP was 10 days vs. 2.7 days reported when cells are exposed to CDV. HDP-CDV seems to circumvent poor cellular uptake by rapid association with cellular membrane phospholipids, whereas CDV uptake proceeds via the slow process of fluid endocytosis.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:240052 CAPLUS

DOCUMENT NUMBER: 137:134473

TITLE: Enhanced inhibition of orthopoxvirus replication in vitro by alkoxyalkyl esters of cidofovir and cyclic cidofovir

AUTHOR(S): Kern, Earl R.; Hartline, Caroll; Harden, Emma; Keith, Kathy; Rodriguez, Natalie; Beadle, James R.; Hostetler, Karl Y.

CORPORATE SOURCE: University of Alabama School of Medicine, Birmingham, AL, USA

SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(4), 991-995
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

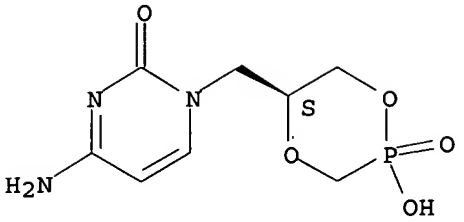
OTHER SOURCE(S): CASREACT 137:134473

IT **127757-45-3P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(enhanced inhibition of orthopoxvirus replication in vitro by alkoxyalkyl esters of cidofovir and cyclic cidofovir)

RN 127757-45-3 CAPLUS

CN 2(1H)-Pyrimidinone, 4-amino-1-[[(5S)-2-hydroxy-2-oxido-1,4,2-dioxaphosphorinan-5-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB The nucleotide phosphonates cidofovir (CDV) and cyclic cidofovir (cCDV) are potent antiviral compds. when administered parenterally but are not well absorbed orally. These compds. have been reported to have activity against orthopoxvirus replication in vitro and in animal models when administered parenterally or by aerosol. To obtain better oral activity, we synthesized a novel series of analogs of CDV and cCDV by esterification with two long-chain **alkoxyalkanols**, 3-hexadecyloxy-1-propanol (HDP-CDV; HDP-cCDV) or 3-octadecyloxy-1-ethanol (ODE-CDV; ODE-cCDV). Their activities were evaluated and compared with those of CDV and cCDV in human foreskin fibroblast (HFF) cells infected with vaccinia virus (VV) or cowpox virus (CV) using a plaque reduction assay. The 50% effective concns. (EC50s) against VV in HFF cells for CDV and cCDV were 46.2 and 50.6 μM compared with 0.84 and 3.8 μM for HDP-CDV and HDP-cCDV, resp. The EC50s for ODE-CDV and ODE-cCDV were 0.20 and 1.1 μM, resp. The HDP analogs were 57- and 13-fold more active than the parent nucleotides, whereas the ODE analogs were 231- and 46-fold more active than the unmodified CDV and cCDV. Similar results were obtained using CV. Cytotoxicity studies indicated that although the analogs were more toxic than the parent nucleotides, the selective index was increased by 4- to 13-fold. These results indicate that the alkoxyalkyl esters of CDV and cCDV have enhanced activity in vitro and need to be evaluated for their oral absorption and efficacy in animal models.

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